REMARKS

Claims 1, 2, 4-22 and 28-36 will be pending upon entry of the above-amendment. Specifically claims 23-27 would be cancelled, without prejudice or disclaimer, and new dependent claims 34-36 would be added. Support for the new claims is found, *inter alia*, on page 3 lines 2 and 21 and/or page 10 line in the second table where batches A-F have pH's ranging from 5.53 to 6.19. Accordingly, no new matter would be introduced by the above-amendment.

Entry of the above-amendment is respectfully requested. Specifically the amendment is believed to place the application into better condition for allowance by canceling independent claim 23 and its sub-claims 24-27. This obviates one of the Examiner's rejections and thus simplifies the issues in the application. The newly presented dependent claims, directed to preferred ranges of pH, require no further consideration and/or search and do not increase the total number of claims (e.g. 5 claims cancelled and only 3 dependent claims added). Accordingly, entry of the amendment places no burden on the Examiner and places the application into better condition for allowance or appeal. Therefore, entry of the amendment is appropriate and is respectfully requested.

**Rejection over Davison**

Claims 1, 2, 4-9, 11, 14-18, and 22 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303). This rejection is respectfully traversed.

Previously, applicants' pointed out that the Examiner's rejection failed to establish a *prima facie* case of obviousness and that, in any event, when the claimed invention was considered as a whole it was clearly unobvious. Because the pH in Davison column 2 related to aqueous solutions of amlodipine salt for injections, it was not a teaching of a solid composition and thus was not the closest prior art to the claimed solid pharmaceutical composition. However, the Examiner dismissed applicants' arguments and continued to criticize the data in the specification as not comparing a pharmaceutical composition having a pH around 7.4 and/or as not being commensurate in scope with the claims. While applicants continue to disagree with many of the Examiner's facts and arguments, in order to conclusively rebut the Examiner's contention, applicants have conducted new tests comparing six different tablets having pH's ranging from 5.19 to 7.2. These tests are submitted herewith in the executed Declaration of Ing. Arlette Vanderheijden, one of the co-inventors of the present application. Entry of the Declaration is requested in that (1) the Declaration responds to a criticism(s) newly raised in the Final rejection, (2) it provides the precise showing requested by the Examiner, and (3) it clearly rebuts and overcomes the Examiner's rejection and places the application into condition for allowance.

Specifically, the Declaration compares four tablets (pH = 5.8, 5.95, 6.07, and 6.36) within the claimed pH range of 5.5 - 6.8 against a tablet composition above (pH = 7.2) and below (pH = 5.19) the claimed range. The tablets were subjected to accelerated stability studies and the results from the 'warm and humid' testing conditions are reproduced below.

Table 2A

Difference in Impurities Between 40°C/75% RH and Baseline After 1 month, Open Dish

| | A<br>pH 7.2 | B<br>pH 6.36 | C<br>pH 6.07 | D<br>pH 5.95 | E<br>pH 5.8 | F<br>pH 5.19 |
|---|---|---|---|---|---|---|
| Δ Aspartate[1] | 5.11 | 1.55 | 0.30 | 0.07 | 0.06 | 0.05 |
| Δ Amide[2] | 0 | 0 | 0 | 0 | 0.04 | 0.13 |
| Δ Pyridine[3] | 0.09 | 0.05 | 0.03 | 0.05 | 0.10 | 0.13 |
| Δ Total Impurities | 5.68 | 1.73 | 0.4 | 0.19 | 0.25 | 0.42 |

1. amlodipine aspartate (Z#204)
2. amlodipine amide (Z#205)
3. amlo-pyridine (Z#202)

The data shows and confirms the overall trend reported in the instant specification, namely that the stability 'sweet spot' for a solid amlodipine maleate is a pH between 5.5 and 6.8. At a pH of 7.2 the amount of aspartate formed significantly increases (see tablet A). As explained on page 3 of the specification, it is believed that the aspartate is formed in the solid composition via a Michael addition, which needs an alkaline environment. On the other hand, as the pH drops below 5.5, the formation of other impurities, such as amlo-pyridine, increases. Thus, applicants are claiming the optimized pH range for reducing the risk of instability.

The data compares a tablet composition that is closer to the presently claimed invention than the hypothetical Davison composition suggested by the Examiner. That is, applicants have compared not merely to a pH of 7.4 but rather have made an even closer comparison using a pH of 7.2 in tablet A. Further, the data is commensurate in scope with the claims. Note that a pH of 6.8 is about half-way between the compared values of 7.2 and 6.36 (tablets A and B, respectively) and less than half-way between the Examiner's proposed 7.4 and the tested 6.36. The trend in the data also supports 6.8 as being a reasonable cut-off. Finally, given the theory of

how the aspartate is formed by way of a reaction requiring alkaline conditions, the 6.8 upper limit is a reasonable scope of protection, i.e. sufficiently less than alkaline to help reduce/avoid aspartate instability issues. Therefore, the data in the Declaration addresses the concerns of the Examiner and shows/confirms the superior results achieved by the present invention.

The data shows not only superior results for the presently claimed invention, but also unexpected/unobvious results. The expectation, following the Examiner's logic, is that tablet A (pH = 7.2) should have been the most stable because it has the pH closest to that of blood. But, under warm and humid accelerated conditions, tablet A has the worst stability. Surprisingly, solid compositions with an acidic pH that is farther removed from that of blood, and within the claimed range of 5.5 - 6.8, provide for enhanced stability performance. Thus, following the 'Davison teaching' to use a pH of around 7.4 contributes to the formation of the aspartate impurity. The superior performance of the claimed compositions having a pH of 5.5 to 6.8 is therefore unexpected.

Indeed, Davison does not teach or suggest that pH of a solid pharmaceutical composition of amlodipine maleate is relevant to stability. Davison teaches in column 2 lines 47-48 that in general stability is important, but fails to teach how to improve stability for any of the salts of amlodipine. Certainly there is no teaching in Davison that controlling the pH of an amlodipine maleate pharmaceutical composition to a range of 5.5 to 6.8 would provide improved stability. And in as much as Davison does not recognize the aspartate impurity, nor its mechanism of formation, Davison likewise offers no suggestion to control pH to the applicants' claimed range or any reasonable expectation of improving stability thereby.

In view of the data in the accompanying Declaration as well as the data in the specification, amlodipine maleate solid compositions having a pH of 5.5 to 6.8 exhibit superior

stability over the hypothetical Davison 'prior art' composition having a pH of 7.2. This improvement was neither obvious nor suggested. Therefore, the presently claimed subject matter is not obvious within the meaning of 35 U.S.C. § 103 and reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection over Davison in view of EP 0089167**

Dependent claims 12 and 13 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of EP 0089167. This rejection is respectfully traversed.

This rejection is in error for at least the reasons set forth above regarding the failures of Davison. Inasmuch as Davison in deficient to render claim 1 unpatentable and EP 0089167 is not asserted to overcome these deficiencies, the instant rejection of dependent claims 12 and 13 is likewise improper. Reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection over Davison in view of Sherwood**

Dependent claims 10, 19 and 20 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of Sherwood et al. (US 5585115). This rejection is respectfully traversed.

This rejection is in error for at least the reasons set forth above regarding the failures of Davison. Inasmuch as Davison in deficient to render claim 1 unpatentable and Sherwood is not asserted to overcome these deficiencies, the instant rejection of dependent claims 10, 19 and 20

is likewise improper. Reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection over Davison in view of Sherwood and further in view of Schobel**

Dependent claim 21 has been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of Sherwood et al. (US 5585115) and further in view of Schobel (US 4687662). This rejection is respectfully traversed.

This rejection is in error for at least the reasons set forth above regarding the failures of Davison. Inasmuch as Davison in deficient to render claim 1 unpatentable and Sherwood and Schobel are not asserted to overcome these deficiencies, the instant rejection of dependent claim 21 is likewise improper. Reconsideration and withdrawal of this rejection are respectfully requested.

**Rejection over Davison in view of Schobel**

Claims 23-27 have been rejected under 35 U.S.C. § 103(a) as allegedly being unobvious over Davison et al. (US 4879303) in view of Schobel (US 4687662). This rejection is respectfully traversed.

While the Examiner has misunderstood the teaching of Schobel, wherein a granulate of excipients and a therapeutic agent is taught to have a particle size of 100 to 600 microns but no teaching regarding the particle size of the therapeutic agent itself is provided, these claims have been cancelled to expedite prosecution. Applicants are considering filing a divisional application directed to this subject matter. Thus, while applicants do not agree with the propriety of this

rejection, the above amendment has nonetheless rendered the rejection moot. Reconsideration and withdrawal thereof are respectfully requested.

**Request for Interview**

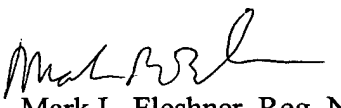
Should the Examiner not find the application in condition for allowance, applicants respectfully request the Examiner to contact applicants' representative, Mark R. Buscher (Reg. No. 35, 006) at 703 502 9440 in order to conduct an interview.

**Conclusion**

In view of the above-amendments and remarks, all claims are directed to novel, patentable subject matter. Reconsideration of the rejections and allowance of the application are respectfully requested.

Please charge any shortage in fees, or any overpayment, in connection with this filing, including extension of time fees, to Deposit Account No. 16-0607.

Respectfully submitted,
Fleshner & Kim, LLP



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Encl: Rule 132 Declaration (executed)